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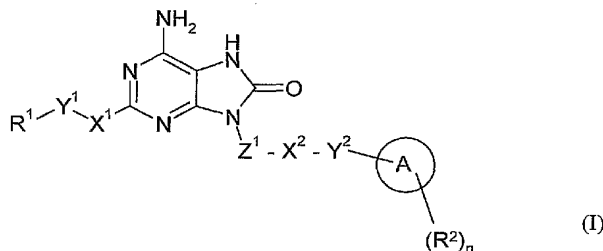
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(54) Title: 8-OXOADENINE DERIVATIVES AS IMMUNO-MODULATORS



(57) Abstract: The present invention provides compounds of formula (I), wherein R^1 , Y^1 , X^1 , Z^1 , X^2 , Y^2 , A , n and R^2 are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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8-OXOADENINE DERIVATIVES AS IMMUNO-MODULATORS

The present invention relates to adenine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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The immune system is comprised of innate and acquired immunity, both of which work cooperatively to protect the host from microbial infections. It has been shown that innate immunity can recognize conserved pathogen-associated molecular patterns through toll-like receptors (TLRs) expressed on the cell surface of immune cells. Recognition of
10 invading pathogens then triggers cytokine production (including interferon alpha(IFN α)) and upregulation of co-stimulatory molecules on phagocytes, leading to modulation of T cell function. Thus, innate immunity is closely linked to acquired immunity and can influence the development and regulation of an acquired response.

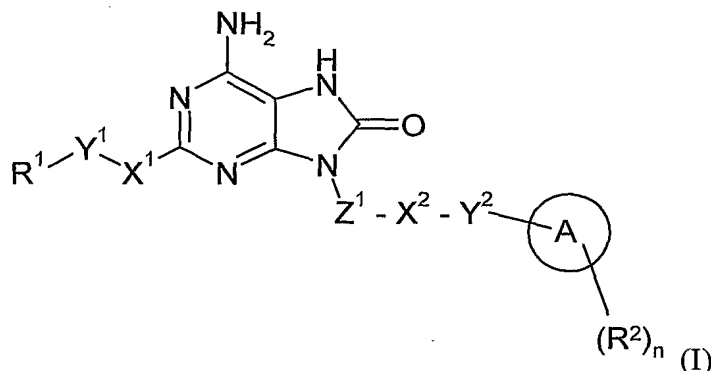
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TLRs are a family of type I transmembrane receptors characterized by an NH₂-terminal extracellular leucine-rich repeat domain (LRR) and a COOH-terminal intracellular tail containing a conserved region called the Toll/IL-1 receptor (TIR) homology domain. The extracellular domain contains a varying number of LRR, which are thought to be involved in ligand binding. Eleven TLRs have been described to date in humans and mice. They
20 differ from each other in ligand specificities, expression patterns, and in the target genes they can induce.

Ligands which act via TLRs (also known as immune response modifiers (IRMS)) have been developed, for example, the imidazoquinoline derivatives described in US Patent No.
25 4689338 which include the product Imiquimod for treating genital warts, and the adenine derivatives described in WO 98/01448 and WO 99/28321.

This patent application describes a class of 9-substituted-8-oxoadenine compounds having immuno-modulating properties which act via TLR7 that are useful in the treatment of viral
30 or allergic diseases and cancers.

In accordance with the present invention, there is therefore provided a compound of formula (I):



wherein

R^1 represents hydrogen, hydroxyl, C_1 - C_6 alkoxy, C_2 - C_5 alkoxycarbonyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, or a C_6 - C_{10} aryl, C_5 - C_{10} heteroaryl or C_3 - C_8 cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_5 alkoxycarbonyl, amino (NH_2) and (di)- C_1 - C_6 alkylamino;

Y^1 represents a single bond or C_1 - C_6 alkylene;

X^1 represents a single bond or an oxygen or sulphur atom or sulphonyl (SO_2) or NR^3 ;

Z^1 represents a C_2 - C_6 alkylene or C_3 - C_8 cycloalkylene group, each of which may be optionally substituted by at least one hydroxyl;

X^2 represents NR^4 , $CONR^4$, NR^4CO , SO_2NR^4 , NR^4CONR^5 or NR^5CONR^4 , SO_2 , CO , NR^5CSNR^5 ;

Y^2 represents a single bond or C_1 - C_6 alkylene;

n is an integer 0, 1 or 2;

each R^2 group independently represents halogen, cyano, $S(O)_mR^9$, OR^{10} , $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, NR^7R^8 , $NR^{10}SO_2R^9$, $NR^{10}CO_2R^9$, $NR^{10}COR^9$, C_6 - C_{10} aryl, C_5 - C_{10} heteroaryl group, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or C_3 - C_8 cycloalkyl group, the latter six groups being optionally substituted by one or more substituents independently selected from halogen, cyano, $S(O)_mR^{12}$, OR^{13} , $SO_2NR^{13}R^{14}$, $CONR^{13}R^{14}$, NR^7R^8 , $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl

R^3 represents hydrogen or C_1 - C_6 alkyl;

R^4 represents hydrogen or a 3- to 8-membered saturated heterocyclic ring comprising a ring group O or NR^6 ;

or R^4 represents a C_1 - C_6 alkylene optionally substituted by one or more substituents independently selected from NR^7R^8 or R^6 ;

R^5 represents hydrogen or a C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl and NR^7R^8 ;

R^6 represents hydrogen, CO_2R^9 , SO_2R^9 , COR^9 , $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, a 3- to 8-membered saturated heterocyclic ring comprising a ring group NR^9 ; or

(i) a C_6 - C_{10} aryl or C_5 - C_{10} heteroaryl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, cyano, oxo, carboxyl, $S(O)_mR^{12}$, OR^{13} , $SO_2NR^{13}R^{14}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, C_1 - C_6 alkyl and C_1 - C_3 haloalkyl, or

(ii) a C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or C_3 - C_8 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, cyano, C_3 - C_8 cycloalkyl, OR^{15} , $S(O)_pR^{16}$, CO_2R^{16} , $NR^{17}R^{18}$, $CONR^{17}R^{18}$, $NR^{17}COR^{16}$, $SO_2NR^{17}R^{18}$, $NR^{17}SO_2R^{16}$ and a group as defined in (i) above;

R^7 , R^8 , R^{13} , R^{14} , R^{15} , R^{19} , R^{20} , R^{22} , R^{23} , R^{24} and R^{25} each independently represent hydrogen, C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl;

or R^7 and R^8 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring comprising a ring nitrogen atom and optionally one or more further heteroatoms independently selected from nitrogen, oxygen, sulphur and sulphonyl, the heterocyclic ring being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR^{21} , $S(O)_qR^{21}$, $NR^{22}R^{23}$, C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl;

R^9 , R^{16} and R^{21} each independently represent a C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, carboxyl, hydroxyl and $NR^{19}R^{20}$;

either R^{10} represents hydrogen or a C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or C_3 - C_8 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR^{21} , $S(O)_qR^{21}$, $NR^{22}R^{23}$ and C_3 - C_8 cycloalkyl, and

R^{11} represents hydrogen or a C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl and $NR^{24}R^{25}$, or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring comprising at least one heteroatom or heterogroup selected from nitrogen, oxygen, sulphur and sulphonyl, the heterocyclic ring being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR^{21} , $S(O)_qR^{21}$, $NR^{22}R^{23}$, C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl;

R^{12} represents C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl;

R^{17} and R^{18} are defined as for R^{10} and R^{11} respectively;

m, p and q each independently represent an integer 0, 1 or 2; and

A represents a monocyclic or bicyclic C_6 - C_{10} aryl or a monocyclic or bicyclic C_5 - C_{12} heteroaryl group containing 1-3 heteroatoms;

or a pharmaceutically acceptable salt thereof.

In the context of the present specification, unless otherwise stated, an alkyl substituent group or an alkyl moiety in a substituent group may be linear or branched. Examples of C₁-C₆ alkyl groups/moieties include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl and n-hexyl. Similarly, an alkylene group/moiety may be linear or branched. Examples of C₁-C₆ alkylene groups/moieties include methylene, ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, 1-methylethylene, 2-methylethylene, 1,2-dimethylethylene, 1-ethylethylene, 2-ethylethylene, 1-, 2- or 3-methylpropylene and 1-, 2- or 3-ethylpropylene. A C₁-C₆ haloalkyl or C₁-C₆ haloalkoxy substituent group/moiety will comprise at least one halogen atom, e.g. one, two, three, four or five halogen atoms, examples of which include trifluoromethyl, trifluoromethoxy or pentafluoroethyl. The alkyl groups in a di-C₁-C₆ alkylamino or alkylcarbonyl group/moiety may be the same as, or different from, one another. A C₁-C₆ hydroxyalkyl or C₁-C₆ hydroxyalkoxy substituent group/moiety will comprise at least one hydroxyl group, e.g. one, two or three hydroxyl groups. An aryl or heteroaryl substituent group/moiety may be monocyclic or polycyclic (e.g. bicyclic or tricyclic) in which the two or more rings are fused. A heteroaryl group/moiety will comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur. Examples of aryl and heteroaryl groups/moieties include phenyl, 1-naphthyl, 2-naphthyl, furyl, thienyl, pyrrolyl, pyridyl, indolyl, isoindolyl, quinolyl, isoquinolyl, pyrazolyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiazolyl and oxazolyl.

A C₂-C₁₀ acyloxy group/moiety is exemplified by a C₂-C₅ alkylcarbonyloxy group, a C₂-C₅ alkenylcarbonyloxy group, a C₂-C₅ alkynylcarbonyloxy group, a C₆-C₉ arylcarbonyloxy group or a C₅-C₉ heteroarylcarbonyloxy group, each of which may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁-C₃ alkoxy or phenyl ring, optionally substituted by from halogen, hydroxyl, cyano, OR²¹, S(O)_qR²¹ or C₁-C₆ alkyl, providing that the total number of carbon atoms in the acyloxy group does not exceed 10.

Preferably R¹ represents hydrogen.

Preferably Y¹ represents C₁-C₆ alkylene, more preferably C₄ alkylene

Preferably X¹ represents oxygen

Preferably Z¹ represents C₂-C₆ alkylene, more preferably (CH₂)₃.

Preferably X² represents NR⁴.

Preferably Y² represents C₁-C₆ alkylene, more preferably a CH₂ group.

Preferably A represents phenyl

- 5 Preferably R² is hydrogen or C₁-C₆ alkoxy

Examples of compounds of the invention include:

6-Amino-9-{3-[benzyl(3-morpholin-4-ylpropyl)amino]propyl}-2-butoxy-7,9-dihydro-8*H*-purin-8-one

- 10 6-Amino-2-butoxy-9-{3-[(4-isopropoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(4-methoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

- 15 6-Amino-2-butoxy-9-{3-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(3,4-dimethoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(4-morpholin-4-ylbenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

- 20 6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)(4-pyrimidin-2-ylbenzyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[[4-(methylthio)benzyl](3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

- 25 6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)[(2-oxo-2*H*-chromen-6-yl)methyl]amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)[(2-oxo-2,3-dihydro-1,3-benzothiazol-6-yl)methyl]amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)(4-propoxybenzyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

- 30 6-Amino-2-butoxy-9-{3-[(3,5-dimethoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(2,4-dimethoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

- 35 (4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](3-morpholin-4-ylpropyl)amino]methyl}phenoxy)acetonitrile

6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)(4-pyrrolidin-1-ylbenzyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)[4-(1*H*-1,2,4-triazol-1-yl)benzyl]amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[[4-(methylsulfonyl)benzyl](3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](3-morpholin-4-ylpropyl)amino]methyl}-*N*-(*tert*-butyl)benzenesulfonamide

5 6-Amino-2-butoxy-9-{3-[[4-(hydroxymethyl)benzyl](3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-9-(3-{benzyl[2-(dimethylamino)ethyl]amino}propyl)-2-butoxy-7,9-dihydro-8*H*-purin-8-one

10 6-Amino-9-{3-[benzyl(1-methylpiperidin-4-yl)amino]propyl}-2-butoxy-7,9-dihydro-8*H*-purin-8-one

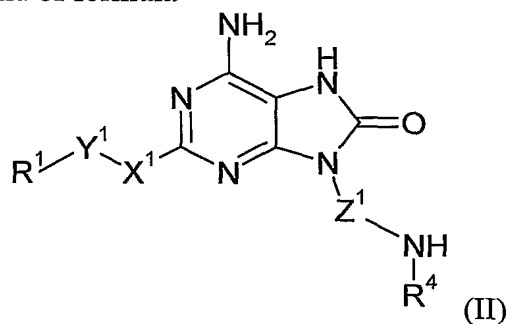
and pharmaceutically acceptable salts or solvates thereof.

The present invention further provides a process for the preparation of a compound of formula (I).

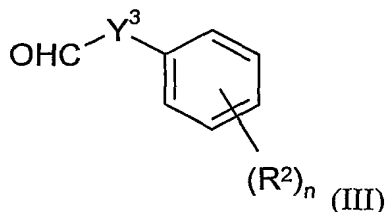
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The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises,

20 (a) reacting a compound of formula

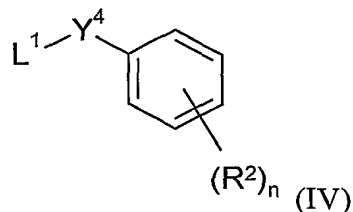


wherein Z¹, Y¹, X¹, R¹ and R⁴ are as defined in formula (I), with a compound of formula



25 wherein Y³ represents a bond or C₁-C₅ alkylene group and n and R² are as defined in formula (I) in the presence of a suitable reducing agent (e.g. sodium triacetoxyborohydride); or

(b) reacting a compound of formula (II) as defined in (a) above with a compound of formula

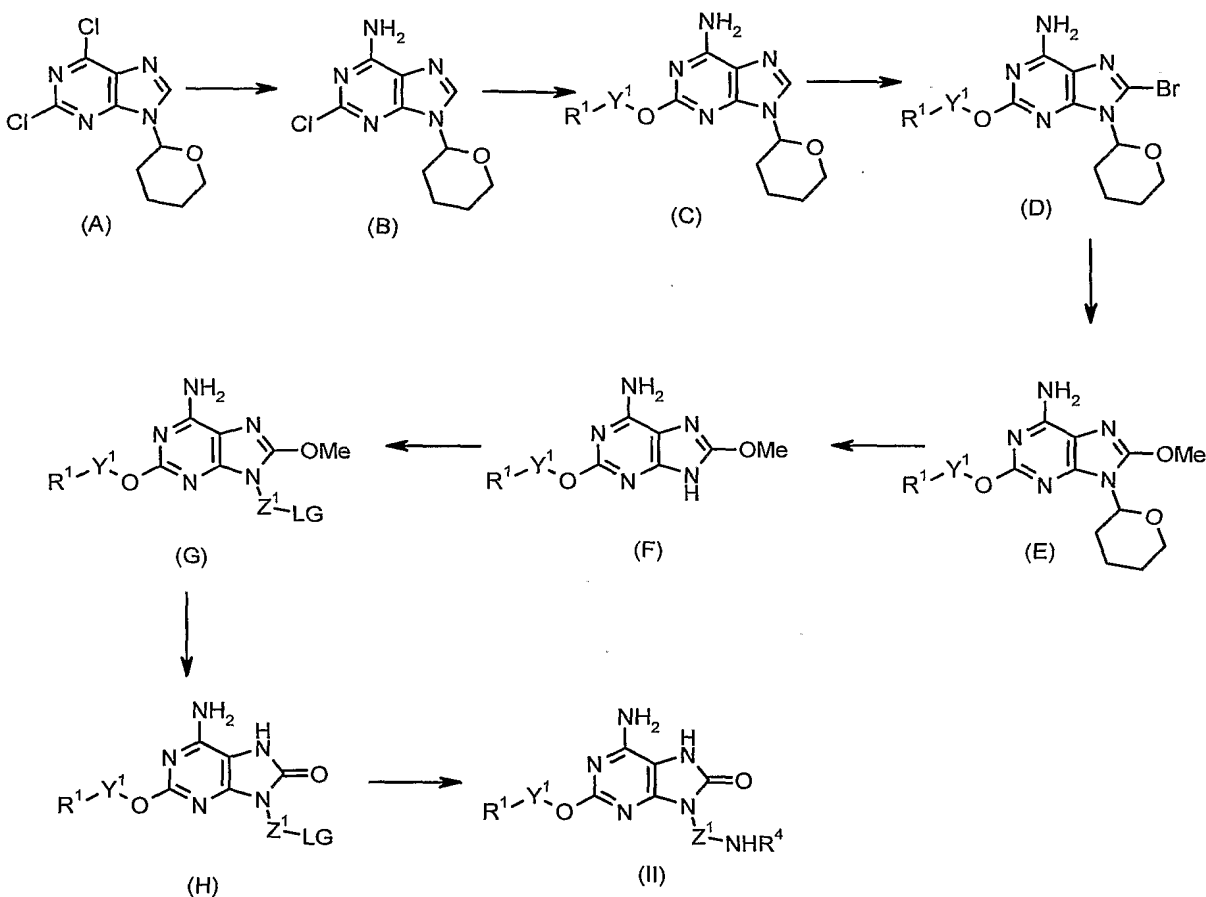


wherein Y^4 represents C_1 - C_5 alkylene group, L^1 represents a leaving group (e.g. halogen, mesylate or triflate) and n and R^2 are as defined in formula (I) in the presence of a suitable base (e.g. sodium carbonate or potassium carbonate); or

In process (a), the reaction may conveniently be carried out in an organic solvent such as 1-methyl-2-pyrrolidinone, 1,2-dichloroethane or tetrahydrofuran at a temperature, for example, in the range from 0 to 150°C.

In process (b), the reaction may conveniently be carried out in an organic solvent such as acetonitrile, 1-methyl-2-pyrrolidinone or *N,N*-dimethylformamide at a temperature, for example, in the range from 0 to 150°C.

Compounds of formula (II) where R^1 represents hydrogen, Y^1 represents C_1 - C_6 alkylene, and X^1 represents oxygen may be prepared as illustrated in the following reaction scheme:



The compound of formula (B) is prepared by reacting the compound of formula (A) with ammonia in an organic solvent such as methanol, ethanol, propanol, butanol, tetrahydrofuran, 1,4-dioxane, diglyme, acetonitrile or an aqueous mixture of any one of the preceding solvents. The reaction may be carried out in an autoclave, and at a temperature, for example, in the range from 20 to 200°C.

Compounds of formula (C) may be prepared by reacting the compound of formula (B) with an alkanol in the presence of a base such as sodium hydride and in an organic solvent such as tetrahydrofuran, 1,4-dioxane, diglyme, *N,N*-dimethylformamide or dimethylsulfoxide, preferably at elevated temperature, e.g. at a temperature in the range from 20 to 150°C. Alternatively an alkali metal such as sodium may be dissolved in the alkanol and then reacted with the compound of formula (B), preferably at elevated temperature, e.g. at a temperature in the range from 20 to 150°C.

Compounds of formula (D) are prepared by brominating a compound of formula (C). The reaction may be carried out using a brominating agent such as bromine, hydroperbromic acid or *N*-bromosuccinimide, in an organic solvent such as carbon tetrachloride, methylene

chloride, dichloroethane, diethyl ether, acetic acid or carbon disulfide. The reaction temperature will generally be in the range from 0°C to the boiling point of the solvent.

Compounds of formula (E) are prepared by reacting a compound of formula (D) with sodium methoxide in an organic solvent such as methanol and at a temperature, for example, in the range from 20 to 150°C.

Compounds of formula (F) may be obtained by treating a compound of formula (E) with an acid such as trifluoroacetic acid in an organic solvent such as methanol.

Compounds of formula (G) are prepared by reacting a compound of formula (F) with a compound of formula LG-Z¹-LG wherein LG represents a leaving group such as a halogen, mesylate or triflate and Z¹ represents a C₂-C₆ alkylene group as defined in formula (II). The reaction may be carried out in an organic solvent such as *N,N*-dimethylformamide, dimethylsulfoxide or acetonitrile with a base present, preferably at room temperature (20°C). A base such as an alkali metal carbonate, e.g. sodium carbonate or potassium carbonate; an alkaline earth metal carbonate, e.g. calcium carbonate; a metal hydroxide, e.g. sodium hydroxide or potassium hydroxide; a metal hydrogenate, e.g. sodium hydride; or a metal alkoxide, e.g. potassium *t*-butoxide, may be used.

Compounds of formula (H) may be obtained by treatment of a compound of formula (G) with an acid. The reaction may be carried out in an organic solvent such as methanol using either an inorganic acid such as hydrochloric acid, hydrobromic acid or sulfuric acid, or an organic acid such as trifluoroacetic acid.

Compounds of formula (II) are prepared by reacting a compound of formula (H) with an amine of formula R⁴NH₂ where R⁴ is as defined in formula (I). The reaction may be carried out in an organic solvent such as acetonitrile or *N,N*-dimethylformamide using an excess of the amine, preferably at elevated temperature, e.g. at a temperature in the range from 0 to 150°C.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective

Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, trifluoroacetate, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

The compounds of formula (I) and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as modulators of toll-like receptor (especially TLR7) activity, and thus may be used in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
2. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-

Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic

conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;

4. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvovaginitis; Peyronie's disease; erectile dysfunction (both male and female);

5. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;

7. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

8. infectious diseases: virus diseases such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, parainfluenza; bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, candida, aspergillus, cryptococcal meningitis, pneumocystis carinii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis.

Thus, the present invention provides a compound of formula (I) or a pharmaceutically-acceptable salt thereof as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

- 5 Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly
10 susceptible to developing the disease or condition.

In particular, the compounds of the invention may be used in the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections and dermatosis.

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The anti-cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

- 20 (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate,
25 cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinese inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);
30 (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of
35 5 α -reductase such as finasteride;
(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-

xyloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; *J. Med. Chem.*, 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase

plasminogen activator receptor function or antibodies to Heparanase);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [HerceptinTM], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (AvastinTM) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-ylxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The invention still further provides a method of treating, or reducing the risk of, an obstructive airways disease or condition (e.g. asthma or COPD) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, the daily dosage of the compound of the invention, if inhaled, may be in the range from 0.05 micrograms per kilogram body weight ($\mu\text{g/kg}$) to 100 micrograms per kilogram body weight ($\mu\text{g/kg}$). Alternatively, if the compound is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight ($\mu\text{g/kg}$) to 100 milligrams per kilogram body weight (mg/kg).

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w,

still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention (including pharmaceutically acceptable salts) may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 micrometres (μm), and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C₈-C₂₀ fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound of the invention with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be

dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The invention therefore further relates to combination therapies wherein a compound of the invention or a pharmaceutical composition or formulation comprising a compound of the invention is administered concurrently or sequentially or as a combined preparation with

another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases COPD, asthma and allergic rhinitis the compounds of the invention may be combined with agents such as tumour necrosis factor alpha (TNF-alpha) inhibitors such as anti-TNF monoclonal antibodies (for example Remicade, CDP-870 and adalimumab) and TNF receptor immunoglobulin molecules (such as Enbrel); non-selective cyclo-oxygenase COX-1/COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate, lefunomide; hydroxychloroquine, d-penicillamine, auranofin or other parenteral or oral gold preparations.

The present invention still further relates to the combination of a compound of the invention and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention and a receptor antagonist for leukotrienes (LT B₄, LTC₄, LTD₄, and LTE₄) selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention and a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention and an anticholinergic agent including muscarinic receptor (M1, M2, and M3) antagonists such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention together with a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol.

The present invention further relates to the combination of a compound of the invention and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to the combination of a compound of the invention and a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12.

The present invention still further relates to the combination of a compound of the invention together with modulators of chemokine receptor function such as antagonists of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX3CR1 for the C-X3-C family.

The present invention still further relates to the combination of a compound of the invention together with a cytokine or modulator of cytokine function, including alpha-, beta-, and gamma-interferon; interleukins (IL) including IL1 to 15, and interleukin antagonists or inhibitors, including agents which act on cytokine signalling pathways.

The present invention still further relates to the combination of a compound of the invention together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (omalizumab).

The present invention further relates to the combination of a compound of the invention and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention further relates to the combination of a compound of the invention together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

A compound of the invention can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

(i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin,

cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);

(ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or idoxifene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuporelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5 α -reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbB2 antibody trastuzumab, or the anti-erbB1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v \beta 3$ function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme

pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or
 (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo
 5 approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

10 The present invention will be further explained by reference to the following illustrative examples.

The following abbreviations are used;

15	EtOAc	ethyl acetate
	DCM	dichloromethane
	NMP	<i>N</i> -methylpyrrolidine
	NBS	<i>N</i> -bromosuccinamide
20	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethylsulfoxide
	THF	tetrahydrofuran
	TFA	trifluoroacetic acid
	mcpba	3-chloroperoxybenzoic acid (Aldrich 77% max)
25	rt	room temperature
	h	hours
	min	minutes
	M	molar
	MS	mass spectrometry
30	APCI	atmospheric pressure chemical ionisation
	NMR	nuclear magnetic resonance
	HCl	hydrochloric acid
	BOC	<i>tertiary</i> -butoxycarbonyl
	HOBt	1-hydroxybenzotriazole
35	EDC	1-(3-dimethylamino propyl)-3-ethylcarbodiimide hydrochloride
	HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate

Unless otherwise stated organic solutions were dried over magnesium sulphate. RPHPLC denotes Reverse Phase Preparative High Performance Liquid Chromatography using Waters Symmetry C8, Xterra or Phenomenex Gemini columns using acetonitrile and either aqueous ammonium acetate, ammonia, formic acid or trifluoroacetic acid as buffer where appropriate. Column chromatography was carried out on silica gel. SCX denotes solid phase extraction with a sulfonic acid sorbent whereby a mixture was absorbed on a sulfonic acid sorbent and eluted with an appropriate solvent such as methanol or acetonitrile and then the free base product was eluted with aqueous ammonia/an appropriate solvent such as methanol or acetonitrile.

Biological Assay

Human TLR7 assay

Recombinant human TLR7 was stably expressed in a HEK293 cell line already stably expressing the pNiFty2-SEAP reporter plasmid; integration of the reporter gene was maintained by selection with the antibiotic zeocin. The most common variant sequence of human TLR7 (represented by the EMBL sequence AF240467) was cloned into the mammalian cell expression vector pUNO and transfected into this reporter cell-line. Transfectants with stable expression were selected using the antibiotic blasticidin. In this reporter cell-line, expression of secreted alkaline phosphatase (SEAP) is controlled by an NFkB/ELAM-1 composite promoter comprising five NFkB sites combined with the proximal ELAM-1 promoter. TLR signaling leads to the translocation of NFkB and activation of the promoter results in expression of the SEAP gene. TLR7-specific activation was assessed by determining the level of SEAP produced following overnight incubation of the cells at 37°C with the standard compound in the presence of 0.1% (v/v) dimethylsulfoxide (DMSO). Concentration dependent induction of SEAP production by compounds was expressed as the log of the minimal effective concentration of compound to induce SEAP release (pMEC).

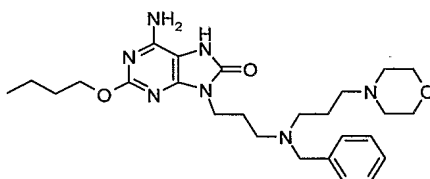
Compound of Example :	8	pMEC	7.2
	12		>7.7
	16		7.4

Experimental

Unless otherwise stated organic solutions were dried over magnesium sulphate. RPHPLC means reversed phase preparative HPLC using Waters Symmetry C8, Xterra, or Phenomenex Gemini columns using acetonitrile and either aqueous ammonium acetate, ammonia, formic acid or trifluoroacetic acid as buffer where appropriate. Column chromatography was carried out on silica gel. Treating with SCX means the mixture was absorbed on SCX and eluted with an appropriate solvent such as methanol or acetonitrile then the free base product eluted with aqueous ammonia/methanol..

Example 1

6-Amino-9-{3-[benzyl(3-morpholin-4-ylpropyl)amino]propyl}-2-butoxy-7,9-dihydro-8H-purin-8-one



(i) 2-Chloro-9-(tetrahydro-2H-pyran-2-yl)- 9H-purin-6-amine

2,6-Dichloro-9-(tetrahydro-2H-pyran-2-yl)- 9H-purine (55g) was dissolved in 7N-aqueous ammonia in methanol (500ml) and heated at 100°C in a sealed flask for 6 hours. The reaction mixture was cooled to room temperature and left overnight. Filtration afforded the subtitle compound. Yield 40g.

¹H NMR δ (CDCl₃) 8.02 (1H, s), 5.94 (2H, brs), 5.71 (1H, dd), 4.15 - 4.22 (1H, m), 3.75 - 3.82 (1H, m), 1.27 - 2.12 (6H, m).

(ii) 2-Butoxy-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine

The product from step (i) (40g) was dissolved in 19%(w/w)-sodium butoxide in butanol (250ml). The reaction mixture was stirred under reflux for 6 hours. The resultant suspension was cooled to room temperature, diluted with water and extracted with diethyl ether. The combined organic phase was washed with water, dried and concentrated *in vacuo*. The subtitle compound was crystallised from diethyl ether/isohexane (1/1, 300ml) and obtained by filtration. Yield 19g.

¹H NMR δ (CDCl₃) 7.87 (1H, s), 5.56 - 5.68 (3H, m), 4.31 - 4.35 (2H, t), 4.14 - 4.17 (1H, m), 3.76 - 3.80 (1H, m), 1.49 - 2.08 (10H, m), 0.98 (3H, t).

5 (iii) 8-Bromo-2-butoxy-9-(tetrahydro-2*H*-pyran-2-yl) 9*H*-purin-6-amine

The product from step (ii) (30g) was dissolved in dry dichloromethane (200ml). The solution was stirred at room temperature whilst *N*-bromosuccinamide (27g) was added portionwise. The mixture was stirred at ambient temperature overnight. 20%(w/v)-Sodium sulfate (200ml) was added and the separated aqueous phase extracted with
10 dichloromethane. The combined organic phase was washed with saturated sodium hydrogen carbonate solution and brine. After concentration *in vacuo*, the residue was dissolved in ethyl acetate, washed with water, brine and dried. The solution was filtered through silica gel and concentrated *in vacuo*. The residue was triturated with diethyl ether
15 and isohexane (1/1, 200ml) then filtered to give the subtitle compound (26g). The filtrate was concentrated *in vacuo* and the residue purified by column chromatography (ethyl acetate/isohexane) to give a further 2.5g of product. The solids were combined to give the subtitle compound as a yellow solid. Yield 28.5g. mp 148-50°C

20 ¹H NMR δ (CDCl₃) 5.59-5.64 (3H, m), 4.32 (2H, m), 4.17 (1H, m), 3.74 (1H, m), 3.08 (1H, m), 2.13 (1H, d), 1.48 - 1.83 (8H, m), 0.98 (3H, t).

25 (iv) 2-Butoxy-8-methoxy-9-(tetrahydro-2*H*-pyran-2-yl) 9*H*-purin-6-amine

Sodium (3.7g) was added to absolute methanol (400ml) under a nitrogen atmosphere. To this solution was added the product from step (iii) (28.5g) and the mixture was stirred at 65°C for 9 hours. The mixture was concentrated *in vacuo* and 500ml of water added. The aqueous phase was extracted with ethyl acetate, washed with brine and dried. The subtitle
30 compound was obtained after crystallisation from diethyl ether. Yield 14.2g.

¹H NMR δ (CDCl₃) 5.51(1H, dd), 5.28 (2H, brs), 4.29 (2H, t), 4.11 - 4.14 (4H, m), 3.70 (1H, m), 2.76 - 2.80 (1H, m), 2.05 (1H, d), 1.47 - 1.81 (8H, m), 0.97 (3H, t).

35

(v) 2-Butoxy-8-methoxy-9*H*-purin-6-amine, TFA salt

The product from step (iv) (24g) was dissolved in absolute methanol (300ml) and 30ml of trifluoroacetic acid was added. The reaction mixture was stirred at ambient temperature for

3 days and concentrated *in vacuo*. The subtitle compound was obtained as a white crystalline solid after trituration with methanol/ethyl acetate. Yield 21g.

¹H NMR δ (CD₃OD) 4.48 (2H, t), 4.15 (3H, s), 1.80 (2H, quintet), 1.50 (2H, sextet), 0.99 (3H, t).

(vi) 9-(3-Bromopropyl)-2-butoxy-8-methoxy-9*H*-purin-6-amine

The product of step (v) (20g) was added in portions over 10 minutes to a rapidly stirred mixture of potassium carbonate (40g) and 1,3-dibromopropane (34ml) in *N,N*-dimethylformamide (250ml) at ambient temperature and the mixture stirred for 1.5 hours. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine and dried. The mixture was purified by column chromatography (ethyl acetate), to afford the subtitle compound as a white solid. Yield 16g.

¹H NMR δ (CDCl₃) 5.19 (2H, s), 4.28 (2H, *J* = 6.7 Hz, t), 4.12 (3H, s), 4.09 (2H, *J* = 9.4 Hz, t), 3.37 (2H, *J* = 13.3 Hz, t), 2.39 - 2.30 (2H, m), 1.81 - 1.72 (2H, m), 1.55 - 1.43 (2H, m), 0.96 (3H, *J* = 11.4 Hz, t).

(vii) 6-Amino-9-(3-bromopropyl)-2-butoxy-7,9-dihydro-8*H*-purin-8-one

The product of step (vi) (35.8g) was dissolved in methanol (400ml) and treated with 4M hydrogen chloride in dioxane (100ml). The mixture was stirred at ambient temperature for 6 hours and concentrated *in vacuo*. Dichloromethane (500ml) was added and concentrated *in vacuo*, which afforded a foam that was taken onto the next step without further purification. Yield 38g.

¹H NMR δ (DMSO-*d*₆) 10.60 (1H, s), 4.45 (2H, m), 3.84 (2H, m), 3.65 (2H, m), 2.19 (2H, m), 1.66 - 1.73 (2H, m), 1.36 - 1.47 (2H, m), 0.96 (3H, m).

(viii) 6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

The product of step (vii) (4g) was suspended in acetonitrile (40ml) and 4-(3-aminopropyl)morpholine (15ml) was added. The mixture was stirred under reflux for 14h.

then the mixture evaporated under reduced pressure. The residue was purified by RPHPLC. Yield 3.59g.

MS: APCI (+ve): 408 (M+H)

(ix) 6-Amino-9-{3-[benzyl(3-morpholin-4-ylpropyl)amino]propyl}-2-butoxy-7,9-dihydro-8*H*-purin-8-one

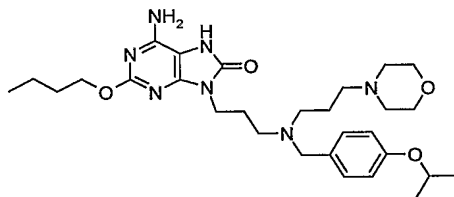
6-Amino-2-butoxy-9-[3-(3-morpholin-4-yl-propylamino)-propyl]-7,9-dihydro-purin-8-one (0.1 g), Benzaldehyde (0.03125 g, 0.03005 ml) were combined in NMP (1.5 mL) and stirred at RT for 15 mins. Sodium triacetoxyborohydride (0.078 g) was added and the reaction mixture was stirred for 16h. The reaction mixture was diluted with methanol and purified by RPHPLC to give the title compound (0.068g)

¹H NMR δ (DMSO-*d*₆) 0.90 (3H, t), 1.31 - 1.42 (2H, m), 1.44 - 1.54 (2H, m), 1.56 - 1.67 (2H, m), 1.77 - 1.88 (2H, m), 2.14 - 2.30 (6H, m), 2.32 - 2.44 (4H, m), 3.43 - 3.52 (6H, m), 3.64 - 3.72 (2H, m), 4.06 - 4.17 (2H, m), 6.37 (2H, s), 7.17 - 7.29 (5H, m), 9.80 (1H, s)
MS: APCI (+ve): 498 (M+H)

Examples 2-16 were prepared by the method of example 1

Example 2

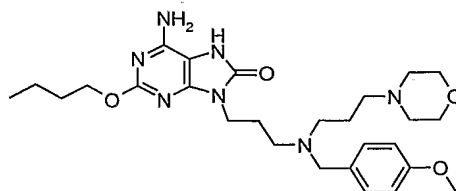
6-Amino-2-butoxy-9-{3-[(4-isopropoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one



¹H NMR δ (DMSO-*d*₆) 0.82 - 0.95 (3H, m), 1.30 - 1.40 (4H, m), 1.43 - 1.53 (2H, m), 1.57 - 1.67 (2H, m), 1.76 - 1.86 (2H, m), 2.15 - 2.24 (3H, m), 2.30 - 2.39 (3H, m), 2.67 (1H, s), 2.99 - 3.09 (4H, m), 3.39 (2H, s), 3.44 - 3.54 (4H, m), 3.61 - 3.77 (6H, m), 4.12 (2H, t), 6.38 (2H, s), 6.82 (2H, d), 7.10 (2H, d)
MS: APCI (+ve): 556 (M+H)

Example 3

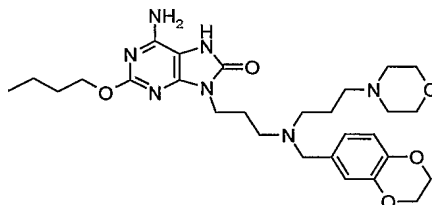
6-Amino-2-butoxy-9-{3-[(4-methoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one



¹H NMR δ (DMSO-*d*₆) 0.90 (3H, t), 1.32 - 1.42 (2H, m), 1.44 - 1.53 (2H, m), 1.57 - 1.66 (2H, m), 1.77 - 1.86 (2H, m), 2.14 - 2.26 (6H, m), 2.29 - 2.42 (4H, m), 3.42 (2H, s), 3.45 - 3.52 (4H, m), 3.63 - 3.71 (2H, m), 3.72 (3H, s), 4.08 - 4.16 (2H, m), 6.38 (2H, s), 6.82 (2H, d), 7.16 (2H, d), 9.82 (1H, s)
MS: APCI (+ve): 528 (M+H)

Example 4

6-Amino-2-butoxy-9-{3-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

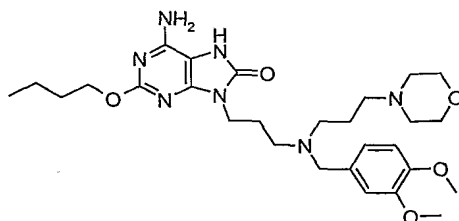


¹H NMR δ (DMSO-*d*₆) 0.90 (3H, t), 1.31 - 1.41 (2H, m), 1.43 - 1.52 (2H, m), 1.57 - 1.66 (2H, m), 1.75 - 1.85 (2H, m), 2.15 - 2.26 (6H, m), 2.29 - 2.41 (6H, m), 3.45 - 3.53 (4H, m), 3.63 - 3.71 (2H, m), 4.12 (2H, t), 4.20 (4H, s), 6.37 (2H, s), 6.66 - 6.77 (3H, m), 9.81 (1H, s)
MS: APCI (+ve): 556 (M+H)

Example 5

6-Amino-2-butoxy-9-{3-[(3,4-dimethoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

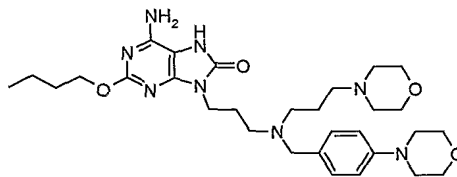
28



¹H NMR δ (DMSO- d_6) 0.90 (3H, t), 1.31 - 1.42 (2H, m), 1.43 - 1.54 (2H, m), 1.55 - 1.65 (2H, m), 1.77 - 1.87 (2H, m), 2.12 - 2.26 (6H, m), 2.30 - 2.44 (4H, m), 3.30 (1H, s), 3.40 - 3.52 (6H, m), 3.65 - 3.76 (7H, m), 4.12 (2H, t), 6.37 (2H, s), 6.73 - 6.77 (1H, m), 6.82 (1H, d), 6.89 (1H, d), 9.81 (1H, s)
 MS: APCI (+ve): 558 (M+H)

Example 6

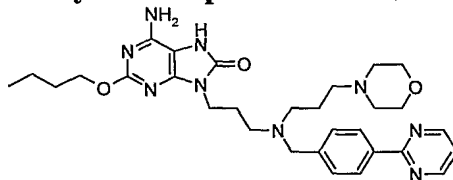
6-Amino-2-butoxy-9-{3-[(4-morpholin-4-ylbenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8H-purin-8-one



¹H NMR δ (DMSO- d_6) 0.82 - 0.95 (3H, m), 1.30 - 1.40 (2H, m), 1.43 - 1.53 (2H, m), 1.57 - 1.67 (2H, m), 1.76 - 1.86 (2H, m), 2.15 - 2.24 (6H, m), 2.30 - 2.39 (4H, m), 2.99 - 3.09 (4H, m), 3.39 (2H, s), 3.44 - 3.54 (4H, m), 3.61 - 3.77 (6H, m), 4.12 (2H, t), 6.38 (2H, s), 6.82 (2H, d), 7.10 (2H, d)
 MS: APCI (+ve): 583 (M+H)

Example 7

6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)(4-pyrimidin-2-ylbenzyl)amino]propyl}-7,9-dihydro-8H-purin-8-one

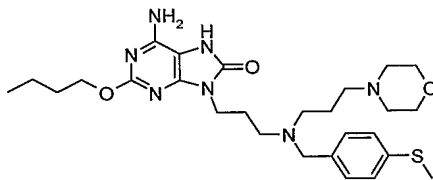


¹H NMR δ (DMSO- d_6) 0.87 (3H, t), 1.28 - 1.39 (2H, m), 1.47 - 1.55 (2H, m), 1.56 - 1.64 (2H, m), 1.82 - 1.90 (2H, m), 2.13 - 2.26 (6H, m), 2.31 - 2.43 (4H, m), 3.46 (4H, t), 3.58

(2H, s), 3.67 - 3.75 (2H, m), 4.11 (2H, t), 6.36 (2H, s), 7.40 - 7.48 (3H, m), 8.32 (2H, d), 8.89 (2H, d), 9.81 (1H, s)
MS: APCI (+ve): 576 (M+H)

Example 8

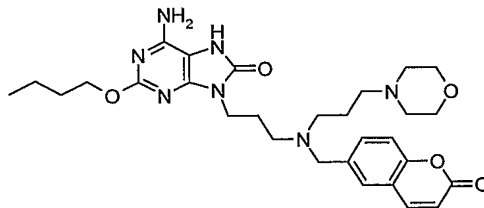
6-Amino-2-butoxy-9-{3-[[4-(methylthio)benzyl](3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8H-purin-8-one



¹H NMR δ (DMSO- d_6) 0.90 (3H, t), 1.29 - 1.41 (2H, m), 1.43 - 1.52 (2H, m), 1.56 - 1.66 (2H, m), 1.78 - 1.87 (2H, m), 2.14 - 2.24 (6H, m), 2.31 - 2.41 (4H, m), 2.44 (3H, s), 3.41 - 3.51 (6H, m), 3.69 (2H, t), 4.12 (2H, t), 6.38 (2H, s), 7.19 (4H, dd), 9.81 (1H, s)
MS: APCI (+ve): 544 (M+H)

Example 9

6-Amino-2-butoxy-9-(3-{(3-morpholin-4-ylpropyl)[(2-oxo-2H-chromen-6-yl)methyl]amino}propyl)-7,9-dihydro-8H-purin-8-one

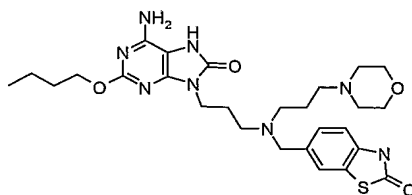


¹H NMR δ (DMSO- d_6) 0.88 (3H, t), 1.28 - 1.39 (2H, m), 1.45 - 1.54 (2H, m), 1.55 - 1.64 (2H, m), 1.79 - 1.88 (2H, m), 2.14 - 2.26 (6H, m), 2.34 - 2.46 (4H, m), 3.45 (4H, t), 3.55 (2H, s), 3.70 (2H, t), 4.10 (2H, t), 6.37 (2H, s), 6.47 (1H, d), 7.31 (1H, d), 7.54 (1H, dd), 7.61 (1H, d), 8.03 (1H, d), 9.80 (1H, s)
MS: APCI (+ve): 566 (M+H)

Example 10

6-Amino-2-butoxy-9-(3-{(3-morpholin-4-ylpropyl)[(2-oxo-2,3-dihydro-1,3-benzothiazol-6-yl)methyl]amino}propyl)-7,9-dihydro-8H-purin-8-one

30

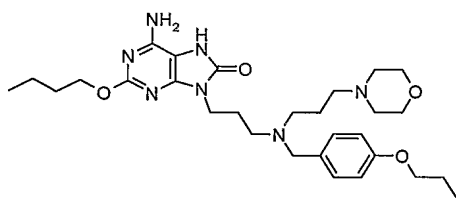


¹H NMR δ (DMSO- d_6) 0.89 (3H, t), 1.26 - 1.41 (2H, m), 1.42 - 1.51 (2H, m), 1.55 - 1.64 (2H, m), 1.76 - 1.89 (2H, m), 2.11 - 2.24 (6H, m), 2.27 - 2.44 (4H, m), 3.40 - 3.53 (6H, m), 3.62 - 3.76 (2H, m), 4.11 (2H, t), 6.37 (2H, s), 7.02 (1H, d), 7.18 (1H, d), 7.45 (1H, s), 9.69 - 9.90 (1H, m)

MS: APCI (+ve): 571 (M+H)

Example 11

6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)(4-propoxybenzyl)amino]propyl}-7,9-dihydro-8H-purin-8-one

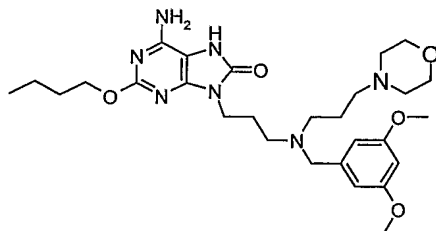


¹H NMR δ (DMSO- d_6) 0.83 - 1.02 (6H, m), 1.29 - 1.43 (2H, m), 1.42 - 1.56 (2H, m), 1.54 - 1.87 (6H, m), 2.12 - 2.26 (6H, m), 2.28 - 2.42 (4H, m), 3.41 (2H, s), 3.43 - 3.53 (4H, m), 3.62 - 3.72 (2H, m), 3.88 (2H, t), 4.12 (2H, t), 6.37 (2H, s), 6.81 (2H, d), 7.15 (2H, d), 9.81 (1H, s)

MS: APCI (+ve): 556 (M+H)

Example 12

6-Amino-2-butoxy-9-{3-[(3,5-dimethoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8H-purin-8-one

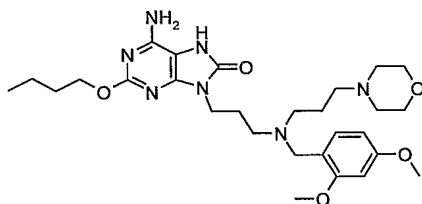


¹H NMR δ (DMSO-d₆) 0.90 (3H, t), 1.32 - 1.40 (2H, m), 1.45 - 1.53 (2H, m), 1.56 - 1.65 (2H, m), 1.77 - 1.85 (2H, m), 2.17 - 2.25 (6H, m), 2.31 - 2.43 (4H, m), 3.44 (2H, s), 3.48 (4H, t), 3.64 - 3.70 (2H, m), 3.71 (6H, s), 4.11 (2H, t), 6.33 (1H, t), 6.38 (2H, s), 6.47 (2H, d)

5 MS: APCI (+ve): 558 (M+H)

Example 13

6-Amino-2-butoxy-9-{3-[(2,4-dimethoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8H-purin-8-one

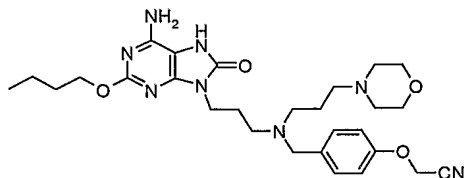


¹H NMR δ (DMSO-d₆) 0.90 (3H, t), 1.30 - 1.41 (2H, m), 1.42 - 1.53 (2H, m), 1.56 - 1.67 (2H, m), 1.75 - 1.86 (2H, m), 2.14 - 2.25 (6H, m), 2.30 - 2.41 (4H, m), 3.40 (2H, s), 3.45 - 3.53 (4H, m), 3.66 (2H, t), 3.73 (6H, s), 4.12 (2H, t), 6.37 (2H, s), 6.39 - 6.44 (1H, m), 6.48 (1H, d), 7.14 (1H, d), 9.80 (1H, s)

15 MS: APCI (+ve): 558 (M+H)

Example 14

(4-[[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl](3-morpholin-4-ylpropyl)amino]methyl]phenoxy)acetonitrile

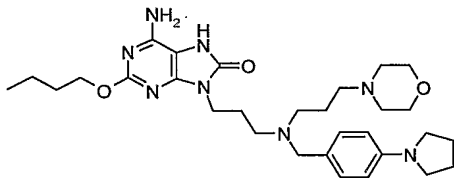


¹H NMR δ (DMSO-d₆) 0.90 (3H, t), 1.30 - 1.42 (2H, m), 1.43 - 1.53 (2H, m), 1.56 - 1.66 (2H, m), 1.77 - 1.86 (2H, m), 2.12 - 2.25 (6H, m), 2.30 - 2.43 (4H, m), 3.42 - 3.51 (6H, m), 3.68 (2H, t), 4.12 (2H, t), 5.13 (2H, s), 6.38 (2H, s), 6.96 (2H, d), 7.26 (2H, d), 9.81 (1H, s)

25 MS: APCI (+ve): 553 (M+H)

Example 15

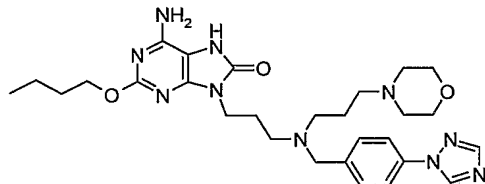
6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)(4-pyrrolidin-1-ylbenzyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one



¹H NMR δ (DMSO-d₆) 0.90 (3H, t), 1.32 - 1.41 (2H, m), 1.44 - 1.53 (2H, m), 1.58 - 1.67 (2H, m), 1.78 - 1.84 (2H, m), 1.90 - 1.96 (4H, m), 2.15 - 2.26 (6H, m), 2.31 - 2.37 (4H, m), 3.15 - 3.21 (4H, m), 3.36 (2H, s), 3.49 (4H, t), 3.67 (2H, t), 4.13 (2H, t), 6.37 (2H, s), 6.42 (2H, d), 7.02 (2H, d), 9.80 (1H, s)
MS: APCI (+ve): 567 (M+H)

Example 16

6-Amino-2-butoxy-9-(3-{(3-morpholin-4-ylpropyl)[4-(1*H*-1,2,4-triazol-1-yl)benzyl]amino}propyl)-7,9-dihydro-8*H*-purin-8-one

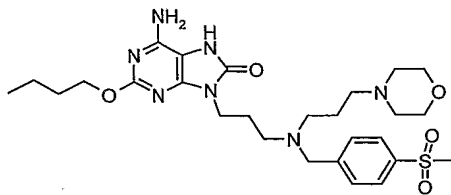


¹H NMR δ (DMSO-d₆) 0.87 (3H, t), 1.28 - 1.39 (2H, m), 1.46 - 1.55 (2H, m), 1.55 - 1.65 (2H, m), 1.80 - 1.90 (2H, m), 2.15 - 2.26 (6H, m), 2.29 - 2.46 (4H, m), 3.41 - 3.51 (4H, m), 3.56 (2H, s), 3.71 (2H, t), 4.10 (2H, t), 6.37 (2H, s), 7.47 (2H, d), 7.76 (2H, d), 8.19 (2H, d), 9.84 (1H, s)
MS: APCI (+ve): 565 (M+H)

Example 17

6-Amino-2-butoxy-9-{3-[[4-(methylsulfonyl)benzyl](3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

33



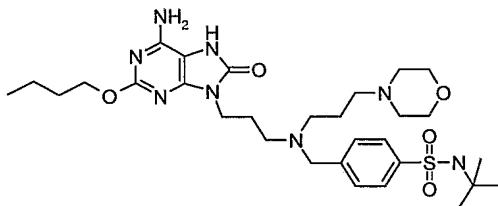
The product from example 1 step (viii) (0.1 g), 4-methylsulphonylbenzyl bromide (0.0673 g) and potassium carbonate (0.0373 g) were combined in DMF (1.5 mL) and stirred at RT for 15 hrs. The reaction mixture was diluted with methanol filtered and purified by RPHPLC to give title compound, 0.039 g

¹H NMR δ (DMSO-d₆) 0.82 - 0.98 (3H, m), 1.27 - 1.43 (2H, m), 1.43 - 1.55 (2H, m), 1.56 - 1.68 (2H, m), 1.79 - 1.91 (2H, m), 2.13 - 2.30 (6H, m), 2.33 - 2.42 (4H, m), 3.18 (4H, s), 3.41 - 3.54 (2H, m), 3.61 (2H, s), 3.66 - 3.79 (2H, m), 4.12 (2H, t), 6.38 (2H, s), 7.57 (2H, d), 7.83 (2H, d), 8.14 (1H, s), 9.82 (1H, s)

MS:APCI (+ve): 576 (M+H)

Example 18

4-[[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl](3-morpholin-4-ylpropyl)amino]methyl]-N-(tert-butyl)benzenesulfonamide



The title compound was prepared using the method of example 17

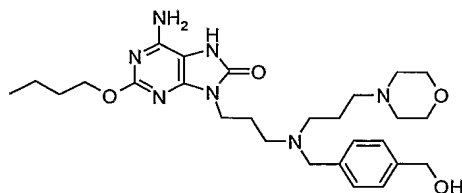
¹H NMR δ (DMSO-d₆) 0.89 (3H, t), 1.06 (9H, s), 1.32 - 1.43 (2H, m), 1.40 - 1.51 (2H, m), 1.54 - 1.69 (2H, m), 1.76 - 1.91 (2H, m), 2.11 - 2.24 (6H, m), 2.25 - 2.40 (4H, m), 3.42 - 3.50 (4H, m), 3.57 (2H, s), 3.64 - 3.78 (2H, m), 4.12 (2H, t), 6.38 (2H, s), 7.39 - 7.53 (3H, m), 7.74 (2H, d), 8.15 (1H, s)

MS:APCI (+ve): 633 (M+H)

Example 19

6-Amino-2-butoxy-9-{3-[[4-(hydroxymethyl)benzyl](3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8H-purin-8-one

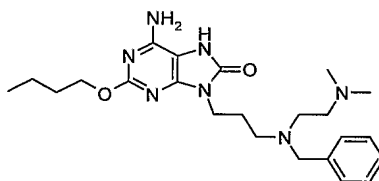
34



^1H NMR δ (DMSO- d_6) 0.90 (3H, t), 1.31 - 1.42 (2H, m), 1.44 - 1.54 (2H, m), 1.56 - 1.67 (2H, m), 1.77 - 1.87 (2H, m), 2.15 - 2.25 (6H, m), 2.30 - 2.42 (4H, m), 3.45 - 3.50 (5H, m), 3.67 (2H, t), 4.13 (2H, t), 4.46 (2H, d), 5.09 (1H, t), 6.37 (2H, s), 7.21 (4H, s), 9.81 (1H, s)
 MS:APCI (+ve): 528 (M+H)

Example 20

6-Amino-9-(3-{benzyl[2-(dimethylamino)ethyl]amino}propyl)-2-butoxy-7,9-dihydro-8H-purin-8-one



(i) 9-(3-Chloropropyl)-2-butoxy-8-methoxy-9H-purin-6-amine

The product of example 1 step (v) (50g) was added in portions over 10 minutes to a rapidly stirred mixture of potassium carbonate (60g) and 1-bromo-3-chloropropane (21ml) in dimethylformamide (400ml) at ambient temperature and the mixture stirred for 3 hours.

The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water and dried. The crude product was recrystallised from acetonitrile. Yield 29.83g.

MS:ESI (+ve): 314

(ii) 6-Amino-9-(3-chloropropyl)-2-butoxy-7,9-dihydro-8H-purin-8-one

The product of step (i) (29.8g) was dissolved in methanol (60ml) and treated with 4M hydrogen chloride in dioxane (60ml). The mixture was stirred at room temperature for 2 hours, cooled to 0°C and neutralised with 3.5% aqueous ammonia solution. The solid was filtered off, washed with water then methanol and dried Yield 27.2g.

¹H NMR δ (DMSO-d₆) 9.88 (1H, s), 6.41 (2H, s), 4.15 (2H, t), 3.80 (2H, t), 3.65 (2H, t), 2.14-2.07 (2H, m), 1.68 - 1.61 (2H, m), 1.43 - 1.34 (2H, m), 0.92 (3H, t).

- 5 (iii) 6-Amino-2-butoxy-9-(3-{[2-(dimethylamino)ethyl]amino}propyl)-7,9-dihydro-8*H*-purin-8-one, hydrochloride

The product of step (ii) (16g), DMSO (16ml) and N,N-dimethylethylenediamine (120ml) was heated at 80°C for 4h then evaporated under reduced pressure. The residue was
10 azeotroped with acetonitrile then heated under reflux in acetonitrile (250ml) for 30min then cooled to 0°C for 1h. The solid was filtered off and dried. Yield 15.32g.

¹H NMR δ (DMSO-d₆) 10.60 (1H, brs), 6.68 (2H, s), 4.15 (2H, t), 3.74 (2H, t), 2.96 (2H, t), 2.97 (2H, t), 2.54-2.51 (2H, m), 2.22 (6H, s), 2.02 - 1.95 (2H, m), 1.68 - 1.61 (2H, m),
15 1.44-1.35 (2H, m), 0.92 (3H, t).
MS: ESI (+ve): 352

- 20 (iv) 6-Amino-9-(3-{benzyl[2-(dimethylamino)ethyl]amino}propyl)-2-butoxy-7,9-dihydro-8*H*-purin-8-one

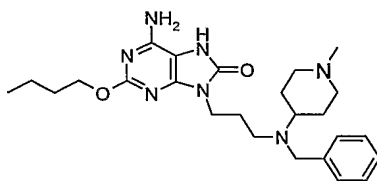
The product from step (iii) (0.1 g) and benzaldehyde (0.0362 g, 0.0347 ml) were combined in NMP (4 mL) and stirred at RT for 15 mins. Sodium triacetoxymethylborohydride (0.0904 g) was added. The reaction mixture was stirred for 16h. The reaction mixture was diluted with
25 methanol and purified by RP-prep-HPLC 75:05 NH₃:acetonitrile over 15 mins to give title compound (0.068g)

¹H NMR δ (DMSO-d₆) 0.90 (3H, t), 1.31 - 1.42 (2H, m), 1.54 - 1.65 (2H, m), 1.77 - 1.88 (2H, m), 2.04 (6H, s), 2.21 - 2.28 (2H, m), 2.39 - 2.47 (4H, m), 3.53 (2H, s), 3.64 - 3.72 (2H, m), 4.12 (2H, t), 6.40 (2H, s), 7.15 - 7.25 (1H, m), 7.28 (4H, s)
30 MS: APCI (+ve): 442 (M+H)

Example 21

35 **6-Amino-9-{3-[benzyl(1-methylpiperidin-4-yl)amino]propyl}-2-butoxy-7,9-dihydro-8*H*-purin-8-one**

36



The title compound was prepared by the method of example 1 using 1-methylpiperidin-4-amine.

5

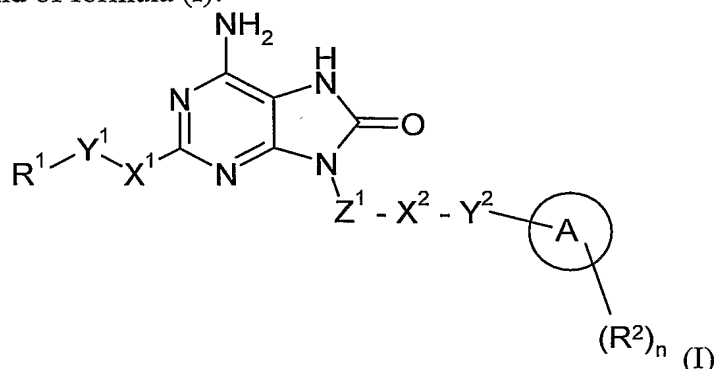
^1H NMR δ (DMSO- d_6) 0.83 - 0.98 (3H, m), 1.30 - 1.54 (4H, m), 1.54 - 1.67 (3H, m), 1.67 - 1.80 (3H, m), 2.09 (4H, s), 2.31 - 2.47 (4H, m), 2.70 - 2.80 (2H, m), 3.55 (2H, s), 3.59 - 3.69 (2H, m), 4.12 (2H, t), 6.36 (2H, s), 7.12 - 7.33 (5H, m), 9.78 (1H, s)

MS:APCI (+ve): 468 (M+H)

10

CLAIMS

1. A compound of formula (I):



5 wherein

R^1 represents hydrogen, hydroxyl, C_1 - C_6 alkoxy, C_2 - C_5 alkoxy carbonyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, or a C_6 - C_{10} aryl, C_5 - C_{10} heteroaryl or C_3 - C_8 cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy,

10 C_1 - C_6 haloalkoxy, C_2 - C_5 alkoxy carbonyl, amino (NH_2) and (di)- C_1 - C_6 alkylamino;

Y^1 represents a single bond or C_1 - C_6 alkylene;

X^1 represents a single bond or an oxygen or sulphur atom or sulphonyl (SO_2) or NR^3 ;

Z^1 represents a C_2 - C_6 alkylene or C_3 - C_8 cycloalkylene group, each of which may be
15 optionally substituted by at least one hydroxyl;

X^2 represents NR^4 , $CONR^4$, NR^4CO , SO_2NR^4 , NR^4CONR^5 or NR^5CONR^4 , SO_2 , CO , NR^5CSNR^5 ;

Y^2 represents a single bond or C_1 - C_6 alkylene;

n is an integer 0, 1 or 2;

20 each R^2 group independently represents halogen, cyano, $S(O)_mR^9$, OR^{10} , $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, NR^7R^8 , $NR^{10}SO_2R^9$, $NR^{10}CO_2R^9$, $NR^{10}COR^9$, C_6 - C_{10} aryl, C_5 - C_{10} heteroaryl group, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or C_3 - C_8 cycloalkyl group, the latter six groups being optionally substituted by one or more substituents independently selected from halogen, cyano, $S(O)_mR^{12}$, OR^{13} , $SO_2NR^{13}R^{14}$, $CONR^{13}R^{14}$,
25 NR^7R^8 , $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl

R^3 represents hydrogen or C_1 - C_6 alkyl;

R^4 represents hydrogen or a 3- to 8-membered saturated heterocyclic ring comprising a ring group O or NR^6 ;

30 or R^4 represents a C_1 - C_6 alkylene optionally substituted by one or more substituents independently selected from NR^7R^8 or R^6 ;

R^5 represents hydrogen or a C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl and NR^7R^8 ;

R^6 represents hydrogen, CO_2R^9 , SO_2R^9 , COR^9 , $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$,

5 a 3- to 8-membered saturated heterocyclic ring comprising a ring group NR^9 ; or
 (i) a C_6 - C_{10} aryl or C_5 - C_{10} heteroaryl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, cyano, oxo, carboxyl, $S(O)_mR^{12}$, OR^{13} , $SO_2NR^{13}R^{14}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, C_1 - C_6 alkyl and C_1 - C_3 haloalkyl, or

10 (ii) a C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or C_3 - C_8 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, cyano, C_3 - C_8 cycloalkyl, OR^{15} , $S(O)_pR^{16}$, CO_2R^{16} , $NR^{17}R^{18}$, $CONR^{17}R^{18}$, $NR^{17}COR^{16}$, $SO_2NR^{17}R^{18}$, $NR^{17}SO_2R^{16}$ and a group as defined in (i) above;

R^7 , R^8 , R^{13} , R^{14} , R^{15} , R^{19} , R^{20} , R^{22} , R^{23} , R^{24} and R^{25} each independently represent
 15 hydrogen, C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl;

or R^7 and R^8 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring comprising a ring nitrogen atom and optionally one or more further heteroatoms independently selected from nitrogen, oxygen, sulphur and sulphonyl, the heterocyclic ring being optionally substituted by one or more
 20 substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR^{21} , $S(O)_qR^{21}$, $NR^{22}R^{23}$, C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl;

R^9 , R^{16} and R^{21} each independently represent a C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, carboxyl, hydroxyl and $NR^{19}R^{20}$;

25 either R^{10} represents hydrogen or a C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or C_3 - C_8 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR^{21} , $S(O)_qR^{21}$, $NR^{22}R^{23}$ and C_3 - C_8 cycloalkyl, and

R^{11} represents hydrogen or a C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from
 30 halogen, hydroxyl and $NR^{24}R^{25}$, or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring comprising at least one heteroatom or heterogroup selected from nitrogen, oxygen, sulphur and sulphonyl, the heterocyclic ring being
 35 optionally substituted by one or more substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR^{21} , $S(O)_qR^{21}$, $NR^{22}R^{23}$, C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl;

R^{12} represents C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl;

R^{17} and R^{18} are defined as for R^{10} and R^{11} respectively;

m, p and q each independently represent an integer 0, 1 or 2; and

A represents a monocyclic or bicyclic C₆-C₁₀ aryl or a monocyclic or bicyclic C₅-C₁₂ heteroaryl group containing 1-3 heteroatoms;

or a pharmaceutically acceptable salt thereof.

5

2. A compound according to claim 1 wherein X¹ represents oxygen.

3. A compound according to claim 1 wherein R¹ represents hydrogen.

10

4. A compound according to claim 1 to 3 wherein Y¹ represents C₁-C₆ alkylene.

5. A compound according to any one of claims 1 to 4 wherein Z¹ is C₂-C₆ alkylene.

6. A compound according to any one of claims 1 to 5 wherein X² represents N-R⁴.

15

7. A compound according to any one of claims 1 to 6 wherein Y² represents C₁-C₆ alkylene.

8. A compound according to any one of claims 1 to 7 wherein A represents phenyl.

20

9. A compound according to claim 1 selected from:

6-Amino-9-{3-[benzyl(3-morpholin-4-ylpropyl)amino]propyl}-2-butoxy-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(4-isopropoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

25

6-Amino-2-butoxy-9-{3-[(4-methoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

30

6-Amino-2-butoxy-9-{3-[(3,4-dimethoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(4-morpholin-4-ylbenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)(4-pyrimidin-2-ylbenzyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

35

6-Amino-2-butoxy-9-{3-[[4-(methylthio)benzyl](3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-{(3-morpholin-4-ylpropyl)[(2-oxo-2*H*-chromen-6-yl)methyl]amino}propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-(3-{(3-morpholin-4-ylpropyl)[(2-oxo-2,3-dihydro-1,3-benzothiazol-6-yl)methyl]amino}propyl)-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)(4-propoxybenzyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

5 6-Amino-2-butoxy-9-{3-[(3,5-dimethoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-{3-[(2,4-dimethoxybenzyl)(3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](3-morpholin-4-ylpropyl)amino]methyl}phenoxy)acetonitrile

6-Amino-2-butoxy-9-{3-[(3-morpholin-4-ylpropyl)(4-pyrrolidin-1-ylbenzyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

6-Amino-2-butoxy-9-(3-{(3-morpholin-4-ylpropyl)[4-(1*H*-1,2,4-triazol-1-yl)benzyl]amino}propyl)-7,9-dihydro-8*H*-purin-8-one

15 6-Amino-2-butoxy-9-{3-[[4-(methylsulfonyl)benzyl](3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](3-morpholin-4-ylpropyl)amino]methyl}-*N*-(*tert*-butyl)benzenesulfonamide

6-Amino-2-butoxy-9-{3-[[4-(hydroxymethyl)benzyl](3-morpholin-4-ylpropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

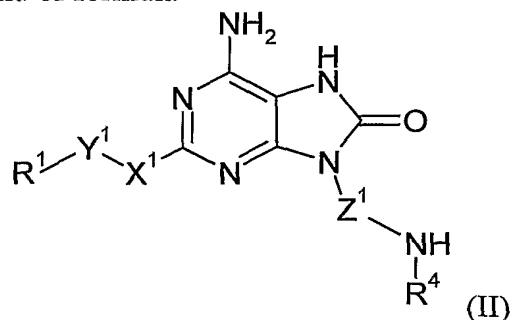
20 6-Amino-9-(3-{benzyl[2-(dimethylamino)ethyl]amino}propyl)-2-butoxy-7,9-dihydro-8*H*-purin-8-one

6-Amino-9-{3-[benzyl(1-methylpiperidin-4-yl)amino]propyl}-2-butoxy-7,9-dihydro-8*H*-purin-8-one

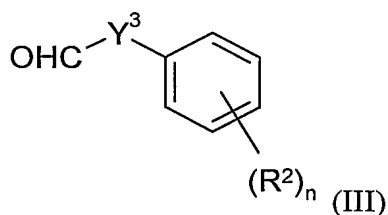
25 and pharmaceutically acceptable salts or solvates thereof.

10. A process for the preparation of a compound of formula (I) where X² represents NR⁴ may be prepared by reacting a compound of formula (II)

30 (a) reacting a compound of formula

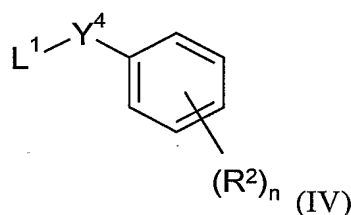


wherein Z¹, Y¹, X¹, R¹ and R⁴ are as defined in formula (I), with a compound of formula



wherein Y^3 represents a bond or C_1 - C_5 alkylene group and n and R^2 are as defined in formula (I) in the presence of a suitable reducing agent (e.g. sodium triacetoxyborohydride); or

(b) reacting a compound of formula (II) as defined in (a) above with a compound of formula



and optionally after carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- removal of any protecting groups
- forming a pharmaceutically acceptable salt of the compound.

11. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 9 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 9 with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9 for use in therapy.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of TLR7 activity is beneficial.

15. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of allergic or viral diseases or cancers.

5 16. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in treating asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections and dermatosis.

10 17. A method of treating, or reducing the risk of, a disease or condition in which modulation of TLR7 activity is beneficial which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9.

15 18. A method of treating, or reducing the risk of, an allergic or viral disease or cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9.

20 19. A method of treating, or reducing the risk of, an obstructive airways disease or condition which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9.

25 20. A pharmaceutical product comprising, in combination, two or more active ingredients including a first active ingredient which is a compound of formula (I) as defined in any one of claims 1 to 9, and a second active ingredient which is selected from:

- a phosphodiesterase inhibitor
- 30 - a β 2 adrenoceptor agonist;
- a modulator of chemokine receptor function;
- an inhibitor of kinase function
- a protease inhibitor
- a glucocorticoid;
- 35 - an anticholinergic agent
- a non-steroidal glucocorticoid receptor agonist.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/004786

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D473/18 A61K31/495 A61P11/00 A61P29/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 728 792 A (DAINIPPON SUMITOMO PHARMA CO [JP]; ASTRAZENECA AB [SE]) 6 December 2006 (2006-12-06) cf. examples, claim 1, paragraph [0006] -----	1-20
A	EP 1 728 793 A (DAINIPPON SUMITOMO PHARMA CO [JP]; ASTRAZENECA AB [SE]) 6 December 2006 (2006-12-06) cf. cpds. (1), examples -----	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

7 March 2008

Date of mailing of the international search report

19/03/2008

Name and mailing address of the ISA/

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Fritz, Martin

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/004786

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2007/004786

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